Journal of Multidisciplinary Engineering Science and Technology (JMEST)
ISSN: 3159-0040
Vol. 1 Issue 5, December - 2014

# A New Technology in Administering Intravenous Drugs - Microneedle Patches

**Khulood Alyamani and Christian Bach**

Department of Biomedical Engineering
University of Bridgeport
Bridgeport,Ct, USA

Kalyaman@my.bridgeport.edu
Cbach@bridgeport.edu

***Abstract*—This model discusses the mechanism of microneedle patch. It shows how this invention could deal with the immune system, benefits, and different methods to overcome challenges. The studies presented in this paper were done to improve previous drug delivery applications by comparing and avoiding their disadvantages. The studies show that patch mechanism, material of various fabrication types, the particulate dosage, site-specific are fundamental factors for effective drug delivery patch, and the acceptability of using the patch. The limitations were how to go through intradermal layer and reach the target shortly and the cost of the patch. This initial paper indicates that microneedle patches for self-administrated against different diseases are applicable and lead to improve the drug delivery field. This paper proves that drug delivery system is complicated and finds an easy and effective method is not impossible and could help people in developing country and saving time.**

***Keywords—component; microneedle; vaccine; transdermal drug delivery; insert (key words)***

## I. INTRODUCTION

Drug delivery plays a key role in medicine and healthcare fields. Controlled drug delivery develops bioavailability by preventing early degradation and stimulating uptake, preserves drug concentration within the therapeutic window by regulating the rate of drug release, and decreases side effects by directing to disease site and target cells (Zhang, Chan, & Leong, 2013).

Transdermal drug delivery, or the delivery of drugs directly into the bloodstream without adversely affecting the skin, has been a major concern for pharmaceutical companies. The traditional transdermal drug delivery makes use of needles and syringes which are at the millimeter scale in terms of diameter and length. Also, Transdermal drug delivery is proper for delivery of medications and can be a valuable alternative to oral route by avoiding the first-pass gut and liver metabolism in gastrointestinal tract. Moreover, the transdermal administration increased consent, controlled plasma levels, and decreased of efficient dose (R., 2004), (M. R. Prausnitz, Mitragotri, S., & Langer, R. , 2004).

A new application called microneedle patch have been introduced as a novel drug delivery application that can capture the appropriateness of a transdermal patch and the efficacy of a hypodermic needle. These needles in micron size have been designated to penetrate typically hundreds of microns into the skin in a painless manner by using the instruments of the microelectronics industry (Martanto, Moore, Couse, & Prausnitz, 2006). Microneedles has surfaced following studies that aim to make transdermal drug delivery easier that self -administration of intravenous drugs could be made more possible with painless and blood-free (Kaushik, 2001), (Bal, Caussin, Pavel, & Bouwstra, 2008), (Van Damme, Oosterhuis-Kafeja, & Van der Wielen, 2009). Microneedles

Microneedles have been invented to enhance skin permeability to allow entry of small-molecule drugs, proteins and vaccines by making micron-scale pathways within the skin's stratum corneum barrier layer (Park, Allen, & Prausnitz, 2005), (Park, Choi, Seo, Choy, & Prausnitz, 2010). The have been many improvements done to the said inventions since its first release in the market. Such improvements include the further miniaturization of needles and patches and using diverse kinds of non-invasive materials for their creation.

Nevertheless, just any other technology, the microneedle patches have its pros and cons of use. Numerous researchers predict that the microneedle patches technology will eventually become more popular than the traditional needle and syringe technology used to administer intravenous drugs, including vaccines in the near future (Hussain, 2014). Hence, it is essential that a good knowledge of the said technology be acquired so as to know what to expect about it. Moreover, the said technology has its limitation, which is also important to understand either for research or application purposes. It should be noted that there are ongoing studies to improve and diversify the use of microneedle patches. It is the objective of this research to make an extensive discussion of what microneedle patches are with a particular focus on its advantages and disadvantages.

### A. Traditional Syringes and Microneedle Patches

Most medications are applied in the form of pills or injections, but these processes of delivery are not always optimal. Drugs taken orally must be absorbed successfully out of the intestine into the bloodstream and resist the enzymatic degradation of the gastrointestinal tract and first pass through the liver. Medications that cannot be taken orally are usually administered by intravenous injection, which lead to the problems of pain, possible contamination, and practice required to apply an injection. Sometimes bolus and injection need to be used more than one time during the day or sustained-release formulation to avoid the toxic and irritating effects of high doses at once and formulation concentration disintegrates at later times (Park et al., 2005).

What a microneedle patch is can be best described or defined by understanding first what a traditional transdermal drug delivery system is. Accordingly, the traditional transdermal delivery system utilizes a syringe and a needle. In this system the needle penetrates the skin up to the nerve-rich regions of the skin. After reaching the said region the drug if pumped out through the syringe. The size of the needle in the traditional transdermal delivery system is in the millimeter range, which means that the length of the needle is at least one millimeter.

This size is necessary so that the needle could penetrate the skin as far as the nerve-rich region, if the needle is too short the drug delivery may fail. Microneedles are smaller than the traditional needles. Their maximum length is not more than 1 millimeter. The decrease in length is also compensated by the decrease in the microneedle's diameter, which is typically within the micro-level as well. The needle alone could not penetrate much through the skin, so what the innovative inventors did was to create a series of microneedles that could puncture the small veins in the non-nerve-rich region of the skin. What the microneedle lack in diameter in length, it compensated it with its number. These series of microneedles are arranged in a patch hence the name microneedle patch for the said invention. Although the principle in creating the microneedles is fairly simple, the benefits that can be derived therefrom are of tantamount importance (Pawar, Pawar, Gadhave, Jadhav, & Gaikwad, 2012).

## II. METHOD

This study utilized secondary data to obtained the information needed to meet the research objectives. The resources used were research articles from international journals, government websites, and education institutions websites. The resources used were also the most current. These inclusion and exclusion criteria for selecting the references were used in order to make sure the data obtained and the findings derived from them would be of high validity and reliability. Validity and reliability are two aspects that are needed to be considered in applying the findings of research in actuality (van der Maaden, Jiskoot, & Bouwstra, 2012).

### A. Fabrication of Microneedle

In the 1990's that the microelectronics industry supplied the microfabrication instruments needed to design microneedles appropriate for pharmaceutical purposes.

Silicon was the first material has been used to fabricate the microneedles by microelectronics industry technology. After that, microneedles have been made out of different materials including ceramic, metal, glass and polymer, and in different shapes and sizes, based on the using of application (Garland et al., 2012).

The fabrication methods of microneedles are depend on (Kim, Park, & Prausnitz, 2012):

1) The prevailing microfabrication techniques of adding.
2) Removing and copying microstructures involving photolithographic procedure.
3) Silicon etching.
4) Laser cutting.
5) Metal electroplating and electropolishing.
6) Micromolding.

### B. Mechanism of Transdermal Delivery

In order to understand in more detail how microneedle patches work, it is necessary first understand the anatomy of the skin. Accordingly, it is the largest organ in the body and has diverse functions. First, it is a barrier from the environment, regulates fluid loss and temperature, and acts as a temperature sensor, immunologic information processor for the immune system. The skin is composed of three layers.

The top most layer is the superficial epidermis, the second layer is the dermis, and the bottom-most layer is called the hypodermis. The top-most layer is about 50 to 150 mm thick. It constantly sheds itself and is largely composed of keratinocytes. It is also at this layer that antigen-presenting cells called the Langerhan's cells can be located. The first 10 to 20 mm thick layer of the epidermis is called the stratum corneum made of stacks of dead, cornified cells called the corneocytes. These cells are flat and are hexagonal in shape with diameters of about 30 mm. These cells are riveted together with proteins and lipids. This layer contains significant amount of water to regulate heat. The dermis constitutes the bulk of the skin. It is predominantly collagen fibers and elastin. It is these components that are responsible for the tensility and elasticity of the skin while at the same time providing support to vascular and nerve network. The dermis rests upon the hypodermis. The hypodermis on the other hand is composed of loose

fatty connective tissues. Unlike the other two layers, its thickness varies across the body even among people (Pawar et al., 2012).

The skin is a profitable mediator for the drug delivery technology for systemic or local effects. However, the natural function of the stratum corneum (SC), which is outermost layer of this tissue, is to provide a barrier to the entry of foreign substance and microorganisms. The studies found that the penetration of some metal particles or other biomaterials has the ability to deliver drugs and the possible disadvantages of the drug through other organ would be decrease (Coulman et al., 2009).

The traditional needles puncture through all three layers up to the nerve reach region, which is immediately below the hypodermis. The cause of this is considerable pain especially when the needle is thick and long. Hence, since the later years of the 1970s, there have been efforts to create miniaturized needles, but the skin structure is one of the stumbling blocks for inventors. Miniaturize needles could not possible puncture through the three layers making the drug delivery less efficient, even wasteful at times. There were two important factors of the design that are considered variables by inventors. These factors are the pressure that the needles could handle and their spread – number of needles needed to make efficient deliveries. Note that these two factors could determine what kind of drug could be delivered, humidity for efficient delivery, delivery pressure, and skin type. In general, therapeutic delivery of drugs using microneedle patches requires that there is many needles penetrate a broad area at the same time. Moreover, the needles have to be very sharp and their ends vary in design (Prausnitz, Mikszta, Cormier, & Andrianov, 2009).

Generally, microneedles can be classified as solid microneedles for tissue pretreatment, dissolving microneedles, drug-coated microneedles, hollow microneedles, and. The drug delivery mechanism of each microneedle is varying by the design.

When microneedles are inserted into the skin, they cause deformation to the skin tissue at the dermis layer where the needles have punctured. This deformation compresses the tissues. The compression results to the reduction of permeability of fluid across the tissue, which is not good for drug delivery as it means that the drug being delivered would not be efficiently distributed through the skin and into the nerve-rich region. This problem with deformation could be easily solved by retracting the needles a little after it had punctured the skin. In other words, what the microneedle patches lack in penetrative ability, it compensate it through the number of needles and its ability to vary the pressure of drug delivery (Prausnitz et al., 2009).

| Type of Microneddle | Mechanism |
|---|---|
| Solid Microneedle | They can be used as a skin pretreatment. A drug composition can be utilized to the skin for slow diffusion of drug through the pores and into the body after injecting and removing the microneedles to create micron-scale pores in the outer skin. A patch can be administrated for passive or iontophoretic delivery across permeablized skin (Martanto et al., 2006). |
| Drug-Coated Microneedle | It is the type of covering the needles with a water-soluble drug formulation. The drug coating starts to dissolve off the microneedles after insertion and diffuse into the skin. After that, the microneedles are removed. Coated microneedles have been used to deliver drugs, proteins, DNA and vaccines for immediate dissolution within the skin (Martanto et al., 2006), (Gill & Prausnitz, 2007). |
| Dissolving Microneedle | It can be fabricated completely free water- soluble or biodegradable polymer that covers the drug within the microneedle matrix. In this process, the microneedles completely dissolve or degrade in the aqueous environment of the skin, that way diffusing the encapsulated drug without sharps waste (Lee, Park, & Prausnitz, 2008). |
| Hollow Microneedle | They can be applied to diffuse liquid into the skin or, to infuse into the skin through the needle bore (Kim et al., 2012). |

### *C. Multiparticulate Dosage*

There have been various designs of microneedle patches. Some of the designs that have been invented allow the gradual and slow injection of medication. This means that the release of drugs into the bloodstream could be controlled at a pace desired by the one using the technology. This means that not all the drugs must be injected at one time.

There are some drugs that require multiple injections to finish. In the traditional method of injection, a patient has the option to stay a clinic or a hospital to finish all the injection sessions that could take hours or he or she could simply return several times to the said clinic. With microneedle's continuous and controlled release functionalities, the patient could simply wear it – the technology is also discrete so it hardly recognizable that a person is wearing it – and allow the technology to do the release at a pace required without human intervention. The patient may do the normal tasks that he or she does every day while having the injection process at work – this saves time and resources (Pawar et al., 2012). One study

used microneedle arrays made from hyaluronic acid. They found that, a continuous decrease of glucose was noticed after 0.25 IU of insulin was administered to skin by microneedles. Moreover, decreased peak plasma insulin levels, but increased plasma insulin concentrations after two hours, were reached with 0.25 IU of insulin administered via microneedles as compared to the insulin syringe of the same dose (Liu et al., 2012).

### *D. Acceptability*

Norman et al. (2014) used two types of questionnaire acceptability and behavioral to determine the consent of the new device. In the questionnaires, the participants had to choose for influenza vaccination between using Intravenous administration, microneedle patch, or no vaccination at all. Also, they asked about three vaccine patch choices: self-administration at home, self-administration under a healthcare professional observation, and healthcare professional administration.

Among those who intended to get vaccinated, 55% answered they'd prefer to self administration at home.12% answered they'd like to use it by healthcare professional and 9% answered they'd like to apply it themselves with a healthcare professional observation. 24% answered they'd prefer to get a flu intradermal injection.

This demonstrates that 76 % would rather use microneedle-patch vaccination instead of (shots) and that 64 % preferred self-administration to vaccination by a healthcare professional. Concerning the impact of price and performance on microneedle patch acceptability, they realized as estimated that acceptability of microneedles reduced if the patch's price increased and on the contrary, increased if volunteers were informed the microneedle patch would be more productive at preventing disease (Norman et al., 2014), (Spendlove, 2014).

Moreover, The World Health Organization determines that 30% of vaccinations in Africa are unsafe on count of cross infection caused by intradermal injection injury. That's a healthcare concern of about $25 per administration. The micrneedle patch has the ability to significantly develop the extent of treatments to those who need them most. Expected to be painless, it only has to be inserted for a minute or so to deliver vaccine to the user. It can be inexpensively fabricated from silicon or polycarbonate for much less than1dollar and uses less than 1% of the standard portion of vaccine. Thus, it is invented to be cheaper and safer than the traditional needle that it promises one day to replace. Furthermore, it is stable in high temperatures and does not need "cold chain", which is the long, costly and sensitive of refrigeration important to transport the vaccines. In developing countries, controlling this cold chain can consume 80% of vaccination operation funds. Also in countries where vaccination is easily to get, people still die because of defect in the cold chain that render the vaccines inefficient (Matsuo et al., 2012). The microneedle patch solves that problem because it doesn't need low temperature to keep its potential (Chen, 2009). The table below shows some of current FDA-approved transdermal drug delivery systems through different types of microneedles patch (Wilson, 2001).

| Year | Generic (Brand) Names | Indication |
|---|---|---|
| 1979 | Scopolamine (Transderm Scop®) | Motion Sickness |
| 1986 | Estradiol (Estraderm®) | Menopausal Symptoms |
| 1999 | Lidocaine (Lidoderm®) | Post-herpetic neuralgia pain |
| 2007 | Rotigotine (Neupro®) | Parkinson's Disease |
| 2010 | Buprenorphine (Butrans®) | Chromic Pain |

## III. EXPLANTION AND DISCUSSION

| | Aim | Studies | Result |
|---|---|---|---|
| **Solid microneedle** (M. R. Prausnitz, 2004) | Success solid microneedles depend on the magnitude of an array to increase transdermal transport for small compounds (e.g: calcein) or large compound (e.g: insulin, bovine serum albumin, and latex nanoparticles). | The microneedles were fabricated by using lithography and reactive ion etching from a silicon wafer. The final needles created a 20-by-20 array, where each needle scaled 80 Am at the base and sharpened to a height of 150 Am with a radius of bending at the tip close to 1 Am. | 1) Solid microneedles could use to deliver different administration like oligonucleotides deliver, Insulin delivery, protein vaccine delivery, and DNA vaccine delivery.<br>2) They interpreted developed transdermal delivery using microneedles and show that skin permeability can be improved by orders of magnitude.<br>3) They show detailed information on process to form needles appropriate for transdermal transport. |

| | | | |
|---|---|---|---|
| **Coated microneedle** (Gill & Prausnitz, 2007) | The efficient of coated microneedles for drug delivery relays on the ability to reliably coat a controlled drug layer onto microneedles. | The initial studies to coat microneedles by submersion into an aqueous drug solution to create patch with no surface coverage. They formulated a coating solution with viscosity enhancer and surfactant and decreased surface tension. | 1) This allowed fully and uniform coverage of the submersion microneedle surface and very versatile. 2) Small molecules, macromolecules and microparticles were all applied as uniform coatings. |
| **Dissolving microneedle** (Lee et al., 2008) | By loading formulation into dissolving microneedles in different methods, researchers were able to create systems from a microneedle patch that attained either bolus or extended release. | To increase drug doses delivery as an extended release and prolong for hours, they integrated formulation into both the microneedles and backing layer or, instead, just the backing layer. Because the backing layer can be large (e.g., 10-100mg) and can be delivered with larger amount of drug, it allows using much larger doses because backing layer mechanical properties have fewer forces. In this process, they hypothesize that formulation can release over time from the drug reservoir in the backing layer and into skin over transdermal pathways made by dissolving microneedles. | The backing layer works as a drug source similar to a conventional matrix-design transdermal patch. |
| **Hollow microneedles** (M. R. Prausnitz, 2004) | Microneedles composed of hollows show the possibility of delivering drugs by diffusion or, by pressure-driven flow for faster delivery. | A variety of hollow microneedles have been fabricated, but only limited work has been published on their possible use to deliver compounds into skin. One study used single microneedles fabricated by glass and pierced into the skin of diabetic animal model in vivo to transport insulin during a 30-min infusion. This study showed a 70% fall in blood glucose level over a five hours period after the insulin was supplied. These needles were designated by a micropipette puller and beveler with a tip radius of 60 Am and were pierced into the skin to a depth of 500– 800 Am. This study finds microneedle-based drug injection into the skin. | This process shown to relieve skin compaction and increase flow conductivity to relax the skin, while the microneedle tip stayed within the skin. |

## IV. Contribution and New Insight

As aforementioned, microneedle patches are so small both in terms of length and diameter. This means that when someone tries to inject drugs, the needles do not enter the skin zone where there are lots of nerves in them. Nerves are the carriers of pain signals to the brain, allowing people to feel pain. Traditional needles cause such pain whenever an injection has to take place. Really long needles, if the one injecting is not an expert, could sometimes go as deep as the bones, which could cause adverse health effects and discomforts to the person being injected with the drugs. Microneedle patches, since they do

not enter the said region of skin, have very little to no pain at all. This means that patients could be administered with their drugs without the discomforts that they could feel with the longer needles. Hence, the primary advantage of microneedle patches is that they are painless (Blain, 2010).

The second advantage is associated with its ease of use and being painful. Due to the fact that it is not painful and has very little danger of being injected to the wrong parts of the body – such as it could touch the bones – microneedle patches are ideal for self-medication or administration of injectable. With microneedle patches, an expert's help is no longer needed in injecting self-medicated drugs. This allows patients to administer drugs unto themselves, practically, wherever they are. Moreover, the microneedle patches are also less accident-prone. The small protrusions of the needles, which are just a few micrometers, make it hard for a patient to commit some accidents that would have detrimental result. Getting puncture accidentally with microneedle patches is less likely to happen compared to the traditional needles and syringes (Escobar-Chavez, 2014).

Still associated with the latter advantage is another benefit that could be derived from using microneedle patches. This benefit is the total reduction of cost of the medication process. While it can be argued that the production microneedle patches cost more than the traditional needles, it can be counter argued that the cost of hiring an expert or going to a clinic to get vaccinated or injected with a medication drug instead of doing it yourself would be a lot more expensive. It is due to this reason and the other advantages aforementioned that the majorities of patients who have heard about or have used this technology are in high acceptance and are demanding the said technology to be applied to broad array of medication (Miseta, 2014).

Nowadays, microneedle arrays have been fabricated from biodegradable materials that fully integrate drugs and vaccines that dissolve in the skin, thereby avoiding sharps waste, such as hypodermic needles (McGrath et al., 2014).

Lastly, there are diverse innovative designs for microneedle patches that patients can choose from. This means that patients would have more and better choices. This fact also allows researchers to further improve the technology in diverse ways. The three-dimensional design and the types of materials that can be used for the needles are just some of the aspect of the microneedles that are continuously being improved (Davidson, Al-Qallaf, & Das, 2008). There are also ongoing studies on the diverse applications of the said technology. Some of these studies are focusing on the use of microneedle patches in vaccines. It is important to note that time is of the essence in cases where a disease outbreak that vaccines be administered fast in order to avoid the increase in casualties. The easy to use characteristics could allow the cutting of time for vaccine administration as it allows personal vaccination (Prausnitz et al., 2009).

There are not much disadvantages associated with microneedle patches except for their cost of production. Note that microneedle patches may require different materials for making them. These materials should be strong enough withstanding pressure despite being so thin. The microneedles are so thin that they might break if material of insufficient strength is used. There are diverse kinds of materials developed at present such as metal alloys and synthetic polymers, which may be applied to different drugs of diverse compositions. This disadvantage is only pronounced if the microneedle path will be used only ones (Escobar-Chavez, 2014).

Another possible disadvantage of the microneedle patches technology is that the delivery time of the drug usually takes more time compared to the traditional needle. This means that the microneedle patches should stay intact to the skin for a relatively longer periods of time compared to the traditional needles. The reason for this is that it takes time for the drugs to travel from the dermis tissues down to the hypodermis and to the nerve-rich region so that it can be efficiently carried through the bloodstream. This means that for instances where immediate deliveries such as for anesthetic uses, the microneedle may not be the best candidate but the traditional needle and syringe (Escobar-Chavez, 2014).

## V. CONCLUSION

Intravenous drugs are essential for medical applications but they cause much pain for the patients. This problem is solved through the invention of microneedle patches. Unlike the traditional needles, the microneedle patches do not puncture the skin up the nerve-rich region. In fact it could only puncture through the dermis layer of the skin. Nevertheless, there are certain challenges that should be addressed in using microneedles. Since the depth of needle penetration is relatively shallower the delivery of drugs becomes slower also. This problem is solved by using an array of microneedles instead of only one. Since the drugs is delivered in a much broader area, the amount of drugs delivered increases. In general, microneedle patches present so many advantages with very few disadvantages. These advantages include: the delivery of drugs is painless, it allows personal drug injection – no need to go to an expert or a clinic, it cost less due to cost reduction in hiring experts, it is discrete so it can be worn in any occasion while undergoing therapeutic injection of drugs, it is safer as it help avoids accidents, etc. There are only two possible disadvantages in using the technology which are: that the needle production may require different kinds of materials to make sure that they are strong, this leads to more expenses in producing the needles; and that the technology does not allow the speedy delivery of drugs into the nerve rich region, hence it cannot be used for instances

where immediate effect of the drug is necessary. It can be concluded therefore that microneedle patches advantages outweighs the disadvantages associated with it. This alone tells us that the prediction of experts and researchers that the technology will greatly spread in the future is valid. It can also be concluded that there are more topics associated with this technology the researchers could venture into so as to make the technology more efficient in performing its functions in providing medical care and healthcare.

## REFERENCES

1. Bal, S. M., Caussin, J., Pavel, S., & Bouwstra, J. A. (2008). In vivo assessment of safety of microneedle arrays in human skin. European Journal of Pharmaceutical Sciences, 35(3), 193-202. doi: http://dx.doi.org/10.1016/j.ejps.2008.06.016

2. Blain, L. (2010). Dissolving microneedle patches – clean, painless, longer-lasting vaccinations. Retrieved from: <http://www.gizmag.com/microneedle-vaccine-patches-longer-lasting/15766/>, accessed: 11/12/2014, 2:14p.m.

3. Chen, X., Prow, T. W., Crichton, M. L., Jenkins, D. W., Roberts, M. S., Frazer, I. H., . & Kendall, M. A. (2009). Dry-coated microprojection array patches for targeted delivery of immunotherapeutics to the skin. Journal of Controlled Release, 139(3), 212-220.

4. Coulman, S. A., Anstey, A., Gateley, C., Morrissey, A., McLoughlin, P., Allender, C., & Birchall, J. C. (2009). Microneedle mediated delivery of nanoparticles into human skin. *International Journal of Pharmaceutics, 366*(1–2), 190-200. doi: http://dx.doi.org/10.1016/j.ijpharm.2008.08.040

5. Davidson, A., Al-Qallaf, B., & Das, D. B. (2008). Transdermal drug delivery by coated microneedles: Geometry effects on effective skin thickness and drug permeability. *Chemical Engineering Research and Design, 86*(11), 1196-1206. doi: http://dx.doi.org/10.1016/j.cherd.2008.06.002

6. Escobar-Chavez, J. J., Bonilla-Martinez, Dalia, Villegas-Gonzalez, Martha Anggelica, and Molina-Trinidad, Eva (2014). Microneedles: a valuable physical enhancer to increase transdermal drug delivery. Retrieved from: <http://www.researchgate.net/publication/49673935_Microneedles_a_valuable_physical_enhancer_to_increase_transdermal_drug_delivery>, accessed: 11/12/2014, 9:43p.m.

7. Garland, M. J., Migalska, K., Tuan-Mahmood, T.-M., Raghu Raj Singh, T., Majithija, R., Caffarel-Salvador, E., . . . Donnelly, R. F. (2012). Influence of skin model on in vitro performance of drug-loaded soluble microneedle arrays. *International Journal of Pharmaceutics, 434*(1–2), 80-89. doi: http://dx.doi.org/10.1016/j.ijpharm.2012.05.069

8. Gill, H. S., & Prausnitz, M. R. (2007). Coated microneedles for transdermal delivery. *Journal of Controlled Release, 117*(2), 227-237. doi: http://dx.doi.org/10.1016/j.jconrel.2006.10.017

9. Hussain. (2014). Microneedle Drug Delivery System: A New Trend in Drug Deliver. Retrieved from: <http://www.pharmainfo.net/pharma-student-magazine/microneedle-drug-delivery-system-new-trend-drug-delivery>, accessed: 11/12/2014, 10:04p.m.

10. Kaushik, S., Allen, H., Donald, D., McAllister, D., Smitra, S., Allen, M., Prausnitz, M. (2001). Lack of pain associated with microfabricated microneedles. Anesth. Analg. 92, 502–504.

11. Kim, Y.-C., Park, J.-H., & Prausnitz, M. R. (2012). Microneedles for drug and vaccine delivery. *Advanced Drug Delivery Reviews, 64*(14),1547-1568.doi:http://dx.doi.org/10.1016/j.addr.2012.04.005

12. Lee, J. W., Park, J.-H., & Prausnitz, M. R. (2008). Dissolving microneedles for transdermal drug delivery. *Biomaterials, 29*(13), 21132124.doi:http://dx.doi.org/10.1016/j.biomaterials.2007.12.048

13. Liu, S., Jin, M.-n., Quan, Y.-s., Kamiyama, F., Katsumi, H., Sakane, T., & Yamamoto, A. (2012). The development and characteristics of novel microneedle arrays fabricated from hyaluronic acid, and their application in the transdermal delivery of insulin. *Journal of Controlled Release, 161*(3), 933-941. doi: http://dx.doi.org/10.1016/j.jconrel.2012.05.030

14. Martanto, W., Moore, J. S., Couse, T., & Prausnitz, M. R. (2006). Mechanism of fluid infusion during microneedle insertion and retraction. *Journal of Controlled Release, 112*(3), 357-361. doi: http://dx.doi.org/10.1016/j.jconrel.2006.02.017

15. Matsuo, K., Yokota, Y., Zhai, Y., Quan, Y.-S., Kamiyama, F., Mukai, Y., . . . Nakagawa, S. (2012). A low-invasive and effective transcutaneous immunization system using a novel dissolving microneedle array for soluble and particulate antigens. *Journal of Controlled Release, 161*(1), 10-17. doi: http://dx.doi.org/10.1016/j.jconrel.2012.01.033

16. McGrath, M. G., Vucen, S., Vrdoljak, A., Kelly, A., O'Mahony, C., Crean, A. M., & Moore, A. (2014). Production of dissolvable microneedles using an atomised spray process: Effect of microneedle composition on skin penetration. *European Journal of Pharmaceutics and Biopharmaceutics, 86*(2), 200-211. doi: http://dx.doi.org/10.1016/j.ejpb.2013.04.023

17. Miseta, E. (2014). Patient Demand, Vaccines, and Drug Delivery: Q&A with Steve Wick of 3M Drug Delivery Systems. Retrieved from: <http://www.outsourcedpharma.com/doc/patient-demand-vaccines-and-drug-delivery-q-a-with-steve-wick-of-m-drug-delivery-systems-0001>, accessed 11/12/2014, 9:51p.m.

18. Norman, J. J., Arya, J. M., McClain, M. A., Frew, P. M., Meltzer, M. I., & Prausnitz, M. R. (2014). Microneedle patches: Usability and acceptability for self-vaccination against influenza. *Vaccine, 32*(16), 1856-1862. doi: http://dx.doi.org/10.1016/j.vaccine.2014.01.076

19. Park, J.-H., Allen, M. G., & Prausnitz, M. R. (2005). Biodegradable polymer microneedles: Fabrication, mechanics and transdermal drug delivery.

20. *Journal of Controlled Release, 104*(1), 51-66. doi: http://dx.doi.org/10.1016/j.jconrel.2005.02.002

21. Park, J.-H., Choi, S.-O., Seo, S., Choy, Y. B., & Prausnitz, M. R. (2010). A microneedle roller for transdermal drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics, 76*(2), 282-289. doi: http://dx.doi.org/10.1016/j.ejpb.2010.07.001

22. Pawar, R., Pawar, S., Gadhave, M., Jadhav, S., & Gaikwad, D. (2012). Microneedles: Novel approach to transdermal drug delivery system. *Journal of drug delivery and therapeutics, 2*(1), 76-80.

23. Prausnitz, M. R., Mitragotri, S., & Langer, R. . (2004). Current status and future potential of transdermal drug delivery. Nature Reviews Drug Discovery, 3(2), 115-124.

24. Prausnitz, M. R. (2004). Microneedles for transdermal drug delivery. *Advanced Drug Delivery Reviews, 56*(5), 581-587. doi: http://dx.doi.org/10.1016/j.addr.2003.10.023.

25. Prausnitz, M. R., Mikszta, J. A., Cormier, M., & Andrianov, A. K. (2009). Microneedle-based vaccines *Vaccines for Pandemic Influenza* (pp. 369-393): Springer.

26. R., L. (2004). Transdermal drug delivery: past progress, current status, and future prospects. Advanced Drug Delivery Reviews, 56(5), 557-558.

27. Spendlove, T. (2014). The Nanopatch Delivers Vaccines without Needles - A Moonshot Project. retrieved from: <http://www.engineering.com/3DPrinting/3DPrintingArticles/ArticleID/6961/The-Nanopatch-Delivers-Vaccines-without-Needles--A-Moonshot-Project.aspx>, accessed: 11/23/2014, 1:14p.m.

28. Van Damme, P., Oosterhuis-Kafeja, F., & Van der Wielen, M., Almagor, Y., Sharon, O., Levin, Y. (2009). Safety and efficacy of a novel microneedle device for dose sparing intradermal influenza vaccination in healthy adults. . *Vaccine, 27*, 454–459.

29. van der Maaden, K., Jiskoot, W., & Bouwstra, J. (2012). Microneedle technologies for (trans)dermal drug and vaccine delivery. *Journal of Controlled Release, 161*(2), 645-655. doi: http://dx.doi.org/10.1016/j.jconrel.2012.01.042

30. Wilson, E. J. (2001). Three generations: The past, present, and future of transdermal drug delivery systems. Pharmacon Inc, 1-22.

31. Zhang, Y., Chan, H. F., & Leong, K. W. (2013). Advanced materials and processing for drug delivery: The past and the future. *Advanced Drug Delivery Reviews, 65*(1), 104-120. doi: http://dx.doi.org/10.1016/j.addr.2012.10.003